IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

US Application of Reese et al

Serial No. 09/914,596

Filed: 15 March, 2000

Title: 2' substituted RNA Preparation

Declaration under Rule 132

I, Mark Edward Douglas, hereby declare as follows:

1. I have been awarded a Bachelor of Sciences degree with Honours in Chemistry from the University of Liverpool, and a Doctorate from the University of Liverpool for research into Oligonucleotide Chemistry. From 1990 to 1995 I was employed as a Staff Scientist at the European Molecular Biology Laboratory, Heidelberg conducting research into the chemistry of modified nucleosides, with particular focus on 2'-O-alkylated ribonucleosides. From 1996 to the present date, I have been employed within the DNA Medicines business of Avecia Limited and its predecessors. During my employment, I have been involved in all aspects of research and development regarding oligonucleotide synthesis, both on laboratory and commercial scales.

2. I have read the description and claims, as amended, of patent application USSN 09/914,596 (the application in suit); the office actions mailed on 20 May, 2003 and 22 January, 2004; Cook et al, WO96/27606 ("Cook"); and McGee et al, Nucleosides and nucleotides (1996) Vol 15 (11 & 12) pp1797-1803 ("McGee").

3. I note that Cook, in example 41, pages 54 to 55, uses tris(2-methoxyethyl) borate under forcing conditions of 155°C to 160°C to achieve a yield of 63% of 2'-O-(2-methoxyethyl)uridine. I also note that Cook, in procedure 3 of example 20 (Page 46) uses trimethylborate to achieve under even more forcing conditions of 175°C for 60 hours to achieve a yield of 100% of 2'-O-(2-methyl)uridine.

4. I note that McGee discloses at page 1796, results 3a-d that the yields for larger alkoxides are substantially lower than those for the simple methoxide. This teaching of McGee is entirely consistent with the results discussed above for Cook.

5. I note that page 7, lines 15 to 25 of the application in suit uses aluminium tri(methyloxyethoxide) in a reaction equivalent to that of Cook in example 41 at pages 54 to 55, the aluminium tri(methyloxyethoxide) being employed in place of the tris(2-methoxy ethyl) borate of Cook, and the temperature being 125°C (the boiling point of 2-methoxyethanol), compared with the 155°C to 160°C of Cook. The yield achieved was 91% of 2'-O-(2-methoxyethyl)uridine.

6. In my opinion, the yield achieved by the process of the application in suit is surprisingly and unexpectedly high, given that the temperature employed is substantially lower than

the equivalent process of Cook. The fact that this yield is so high is even more unexpected given the teaching of McGee that larger alkoxides produce significantly lower yields than the smallest alkoxides. In my opinion, the process of the present invention utilising the aluminium-based $Al(OR)_3$ instead of the conventional boron-based $B(OR)_3$ demonstrates an unexpected technical advantage over the teaching of Cook and McGee.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made upon information and belief are believed to be true; and further, that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC 1001, and that such wilful false statements may jeopardise the validity of the application and any patent issuing thereon.

Date: 13th July, 2004

Mark Edward Douglas